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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/778,259	02/07/2001	Cristobal Guillermo dos Remedios	13388	4496

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EXAMINER

CHEU, CHANGHWA J

ART UNIT	PAPER NUMBER
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1641

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 09/778,259	Applicant(s) REMEDIOS ET AL.	
	Examiner JACOB CHEU	Art Unit 1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 07 August 2008.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 38 and 42-47 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 38 and 42-47 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>8/4/2008</u> . | 6) <input type="checkbox"/> Other: _____ |

Art Unit: 1641

DETAILED ACTION

1. Applicant's amendment and Rule 1.132 affidavits filed on 8/7/2008 have been received and entered into record and considered.

The following information provided in the amendment affects the instant application:

Claims 1-37, 39-41 are cancelled.

Currently, claims 38, 42-47 are under examination.

The new rejections of claims 38, 42-47 are set forth below.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

3. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Art Unit: 1641

4. Claims 38, 42-43 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Richardson et al. (Environ Mutagenesis 1981 Vol. 3, page 545-553) in view of Griffith et al. (US 5354996).

Richardson et al. teach a method of detecting toxic mutagens and carcinogens, including Pb^{+2} , Zn^{+2} , Cd^{+2} , Fe^{+2} and Pt^{+2} (See Abstract; Figure 1 and Table II) (Note, these are metal ions). Richardson et al. teach contacting samples containing the metal ions with nucleic acid molecules intercalated with a fluorescent dye, and detecting the dissociating of the binding between the nucleic acid molecules and said fluorescent dye, wherein said dissociation of the binding is indicative of the presence of the metal ions (See Table II; Figure 1; page 546, last paragraph to page 547, first paragraph for "Acridine Orange Displacement Assay"). The assay taught by Richardson et al. can detect these ions in the range of micromolar amounts. *supra*. It is noted that Pb^{+2} , Zn^{+2} , Cd^{+2} , Fe^{+2} and Pt^{+2} also exist in the environment and associated with cancer (See page 545, Introduction; also the listed epidemiological studies by Sunderman, 1978). However, the samples measured by Richardson et al. are from laboratory, not an "environmental samples".

Griffith et al. view of the contamination and pollution of heavy metal ions in the environment, and the need of measuring and monitoring the levels of these heavy metals for public safety and health (Col. 1-25). Particularly, Griffith et al. teach method of measuring the aquatic samples, e.g. waste water (Figure 1 and Figure 2).

Therefore, it would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made to have motivated Richardson et al. to apply the method of detection of metals to the monitoring of the environmental aquatic samples as taught by Griffith et al. to monitor heavy metal ions in the aquatic samples. One ordinary skill in the art would have been motivated to do so because public safety and health concern about the pollutions from the ubiquitous heavy metals in our ecosystem.

Art Unit: 1641

With respect to claim 42, the metal ion detected is a heavy metal, such as cadimium and platinum. (See Richardson et al.; page 545).

With respect to claim 43, the fluorescent dye used by Richardson et al. is the acridine orange. Supra.

5. Claims 44-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Richardson et al. in view of Griffith et al., as applied to claim , 42-43 and 47 above, and further in view of Nikiforov et al. (US 5610287).

Richardson and Griffith et al. references have been discussed but no explicit teaching on immobilizing DNA on a solid substrate is mentioned.

Nikiforov et al. teach immobilizing DNA molecules on the substrate of a 96-well microtiter plate to improve analysis in a rapid, convenient and inexpensive manner (Col. 4, line 10-20).

Therefore, it would have been prima facie obvious to one ordinary skill in the art at the time the invention was made to motivated Richardson and Griffith et al. to immobilize DNA molecules on the substrate of a 96-well microtiter as taught by Nikiforov et al. to detect mass samples. One artisan in the field would have been motivated to do so in order to take advantage of time and cost saving.

With respect to claims 44-45, Nikiforov et al. teach the materials for microtiter includes polystyrene (Col. 4, line 33-36).

Response to Applicant's Arguments

Art Unit: 1641

6. Applicant's arguments with respect to claims 38, 42-47 have been considered but are moot in view of the new ground(s) of rejection (Note: it is now 35 USC 103 (a) instead of 35 USC 102 (b); See below).

7. Although the new ground of rejection set forth in this Office Action, the main reference of Richardson et al. is still applicable as discussed below.

8. In addition, the affidavit under 37 CFR 1.132 filed 8/7/2008 is insufficient to overcome the rejection of claims 38, 42-47 based upon Richardson et al. in view of Griffith et al. as set forth in the this Office action (also see below).

Applicant argues that Richardson et al. reference relates to the measurement of heavy metal ions in a "laboratory-contrived solution", whereas the instant invention directs to a method of measuring the heavy metal ions in an "aquatic, terrestrial, gaseous, or industrial environmental samples. Applicant also submits EPA (Environmental Protection Agency) definition on "environmental samples" in support of the arguments (See Exhibits 1-2). Applicant also argues that Richardson et al. teach measuring heavy metal ion independently, i.e. each metal was measured at one time, whereas the current method detects multiple metal ions at the same time.

Applicant's arguments have been considered, but are not persuasive.

With respect to the "environmental samples", Examiner has provided a secondary reference (Griffith et al.) in this Office Action for motivation/or suggestion to motivate one ordinary skill in the art such as Richardson et al. to apply the detection of metal ions in "environmental samples".

With respect to the arguments on the detection of multiple heavy metal ions at one time, the claim language does not recite such a feature. The amended claim is shown below:

Art Unit: 1641

38. (Currently Amended) A method for detecting the presence of micromolar amounts of ~~[[a]]~~ toxicant metal ions in an ~~aquatic, terrestrial, or industrial~~ environmental sample, ~~wherein the toxicant is a metal ion~~, said method comprising obtaining an aquatic, terrestrial, gaseous or industrial environmental sample; contacting said sample putatively containing said ~~toxicant~~ metal ions with a nucleic acid molecule intercalated with a fluorescent dye; and screening for dissociation of binding between said nucleic acid molecule and said dye, wherein said dissociation of binding is indicative of the presence of said toxicant micromolar amounts of said metal ions.

It appears that the instant claim merely recites that the claimed method is capable of detecting multiple heavy metal ions which is also fully disclosed by Richardson et al. since Richardson et al. disclose detection of various metal ions, including Pb^{+2} , Zn^{+2} , Cd^{+2} , Fe^{+2} and Pt^{+2} (See Table II). The recited claim language does not preclude detecting different single heavy metal ion at different time.

Furthermore, Applicant argues that the instant method provides a rapid, accuracy and unexpected assay as asserted by the inventor (See Declaration of Dr. Cristobal Guillermo dos Remedios- inventor of this application). In addition, Applicant argues that the conventional method of determining heavy metals in the environment often uses live whole organism or cell-based methods where the toxicity of an environmental sample is determined by assessing the effect of sample exposure on the viability and/or phenotype of the organism/cell (See Declaration paragraph 8 and 10). Instead of relying on the overall intact cellular level, the instant method focuses on the “molecular-based system, e.g. nucleic acid based level” to determine the level of heavy metal ion from the environmental samples. Applicant also argues that the existing multiple heavy metals in one sample may exert synergistic or antagonistic effects on the toxicity of the samples (See Declaration paragraph 11 and 12). Applicant argues that the prevailing view in the

Art Unit: 1641

art at the time of the conception of the present invention was that synergistic or antagonistic effects of multiple metal toxicants could only be measured with live whole organism or cell-based system. Nevertheless, the instant invention has unexpectedly shown that a naked nucleic acid based assay is able to detect synergy and antagonism in mixtures of metals.

Applicant's arguments have been considered, but are not persuasive.

With respect to the convenience of the instant method, the method taught by Richardson et al. can also be considered rapid and accurate because similar steps are used by both Applicant and Richardson et al..

With respect to the arguments on the availability of multiple detections of heavy metals in the sample, Examiner has discussed above that the claim language does not preclude detecting different metals at different time. Moreover, in view of Griffith et al. (secondary reference used in 35 USC 103 (a)), one ordinary skill in the art would have knowledge that at least, Pb^{+2} , Zn^{+2} , Cd^{+2} , Fe^{+2} and Pt^{+2} metal ions, are all capable of displacing the fluorescent dye from the nucleic acid (See Table II displacement data for each metal)(emphasis added). Therefore, when combining both Richardson and Griffith et al. teachings, one artisan in the field would have expected to observe the displacement fluorescent dyes from the environmental samples in the presence of all Pb^{+2} , Zn^{+2} , Cd^{+2} , Fe^{+2} and Pt^{+2} (emphasis added). Thus, multiple heavy metal ions from a sample can also be detected.

In addition, Examiner would like to point out that the so-called synergistic or antagonistic toxicity is not a recited feature in the claim language. Still, if the method discloses substantially similar method, it would also capable of performing the same purported function, i.e. reflecting synergistic or antagonistic toxicity. Finally, with respect to the asserted novel “molecular basis nucleic acid assay” as compared to the conventional live whole organism or cell-based system, the reference of Richardson et al. proves its

Art Unit: 1641

obviousness since using “nucleic acid” for detection of metal ions in a sample has been known since 1981 by Richardson et al. as set forth in this Office Action.

Conclusion

9. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JACOB CHEU whose telephone number is (571)272-0814. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner’s supervisor, Mark Shibuya can be reached on 571-272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jacob Cheu/

Examiner, Art Unit 1641

/Mark L. Shibuya/
Supervisory Patent Examiner, Art Unit 1641